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(21) International Application Number: PCT/CA94/00669 (22) International Filing Date: 6 December 1994 (06.12.94) (30) Priority Data: 08/162,478 7 December 1993 (07.12.93) US (71) Applicant: SYNPHAR LABORATORIES, INC. [CA/CA]; #24 Taiho Alberta Center, 4290-91A Street, Edmonton, Alberta T6E 5V2 (CA). (72) Inventors: MAITI, Samarendra, Nath; 6756-39 Avenue, Ed- monton, Alberta T6K 1T8 (CA). FLAKPUI, Charles, Yao; 188 South Ridge, Edmonton, Alberta T6H 4M9 (CA). REDDY, Andhe, Venkat, Narendra; 1503-104 Street, Ed- monton, Alberta T6J 5T2 (CA). CZAJKOWSKI, David, Paul; 3819-86 Street, Edmonton, Alberta T6K 0H7 (CA). MICETICH, Ronald, George; 12 Braeside Terrace, Sher- wood Park, Alberta T8A 3V6 (CA). (74) Agent: RICHES, MCKENZIE & HERBERT; Suite 2900, 2 Bloor Street East, Toronto, Ontario M4W 3J5 (CA).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i>
(54) Title: 2-SPIRO(2'-SPIROCYCLOALKYL)CYCLOPROPYL CEPHALOSPORIN SULFONES AS ANTIINFLAMMATORY AND ANTIDEGENERATIVE AGENTS (57) Abstract 2-spiro(2'-spirocycloalkyl)cyclopropyl cephalosporin sulfone compounds, methods of treating patients for elastase inhibition, and processes for preparing such compounds.		

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**2-Spiro(2'-spirocycloalkyl)cyclopropyl Cephalosporin Sulfones
as Antiinflammatory and Antidegenerative Agents**

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FIELD OF THE INVENTION

The present invention relates to novel 2-spiro(2'-spirocycloalkyl)cyclopropyl cephalosporin sulfone derivatives as potent elastase inhibitors and to processes for their preparation.

10

BACKGROUND OF THE INVENTION

Human leukocyte elastase (HLE) is a member of the family of serine proteases. It is carried by the azurophilic granules of human polymorphonuclear leukocytes and released into the extracellular space. Elastase, like other serine proteases, have a catalytic triad composed of three juxtaposed amino acid residues : aspartate (Asp-102), histidine (His-57), and serine (Ser-195). Through either a "charge relay" or a "proton relay" mechanism, the three residues catalyze a proton extraction via oxyanion attack (ser-195) on an amide carbonyl group. The end result of this reaction is a degradation of peptide bonds.

Under normal conditions, the proteolytic activity of HLE is controlled by several natural protease inhibitors. The primary guardian against connective tissue destruction is α -1 protease inhibitor (α -PI). Although α -PI associates with HLE very quickly and irreversibly, several pathological conditions may arise when α -PI levels are genetically low, or when α -PI has been oxidized or degraded, or when access to HLE is restricted. The disease states resulting from uncontrolled elastase activity include: pulmonary emphysema, rheumatoid arthritis, adult respiratory distress syndrome (ARDS), cystic fibrosis, and other related syndromes.

35

SUMMARY OF THE INVENTION

The present inventors synthesized 7 α -substituted 2-spiro(2'-spirocyclo- alkyl)- cyclopropyl cephem sulfones and found from studies that these compounds are potent elastase inhibitors and that they are useful in the

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prevention, control and treatment of inflammatory conditions, particularly rheumatoid arthritis, osteoarthritis, cystic fibrosis, chronic bronchitis and emphysema.

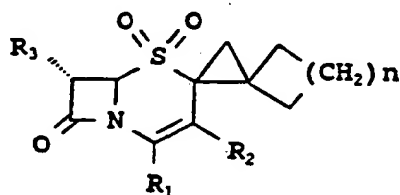
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DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided novel 7 α -substituted 2-spiro(2'-spirocycloalkyl) cyclopropyl cephalosporin sulfones having anti-elastase activity. Such derivatives, or elastase inhibitors, are useful in the prevention, control and treatment of inflammatory conditions, particularly emphysema, rheumatoid arthritis, osteoarthritis and cystic fibrosis, chronic bronchitis and emphysema.

In one aspect, the present invention relates to a 7 α -substituted 2-spiro(2'-spirocycloalkyl)cyclopropyl cephalosporin sulfone of the structural formula (I):

20



.... (I)

25

Wherein R_1 is COOR_4 , COR_5 , $-\text{C}(\text{R}_5)=\text{N}-\text{OR}_6$, CONR_7R_8 ; R_4 is hydrogen; C_{1-6} branched or straight alkyl; C_{2-6} alkenyl; C_{1-6} alkanoyl C_{1-6} alkyl; C_{1-6} alkanoyloxy C_{1-6} alkyl; C_{1-6} alkoxy C_{1-6} alkyl; halogenated C_{1-6} alkyl; $-\text{CH}_2$ -phenyl; $-\text{CH}(\text{phenyl})_2$; the phenyl groups may further be substituted with at least one of C_{1-6} alkyl, C_{1-6} alkoxy, nitro.

The preferred groups representing R_4 include hydrogen, methyl, ethyl, tert-butyl, allyl, methoxyethyl, benzhydryl, benzyl, p-nitrobenzyl, p-methoxybenzyl, 2,2,2-trichloroethyl.

R_5 is hydrogen; C_{1-6} straight or branched alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; C_{3-6} cycloalkyl; C_{6-10} aryl; aralkyl; a monocyclic or fused polycyclic saturated or unsaturated heterocyclic group containing from 1 to 4 of any one or more of the heteroatoms selected from N, S and O.

The preferred groups representing R_5 include hydrogen, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethenyl, propenyl, ethynyl, phenyl, benzyl, thienyl, furyl, pyridyl, pyrimidinyl, imidazolyl, triazinyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl.

The substituent R_5 in the formula $-C(R_5)=N-OR_6$ has the same meaning as described above.

The substituent R_6 is hydrogen or a hydrocarbon residue which may be substituted. In the formula $-C(R_5)=N-OR_6$, the OR_6 group may be in "syn" or "anti" configuration. The hydrocarbon residue may be exemplified by C_{1-6} straight or branched alkyl, C_{2-6} alkenyl and C_{3-6} cycloalkyl group.

Substituents of these hydrocarbon residues may be exemplified by hydroxyl group, C_{3-6} cycloalkyl group, mercapto group, amino group, halogen atom, cyano group, carboxyl group, C_{1-3} alkoxy carbonyl group, C_{6-10} aryloxy carbonyl group, C_{7-12} aralkyloxy carbonyl group, C_{3-5} alkenyloxy carbonyl group, C_{6-10} aryl group, a 5- (or 6-) membered heterocyclic group containing from 1 to 4 of any one or more of the heteroatoms selected from N, S and O (examples of which include but are not limited to thienyl, furyl, pyridyl, pyrimidinyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, and the like).

The number of the substituents on the above mentioned hydrocarbon residue is not restricted to one and may be plural which are the same or different.

More preferred examples of the substituted hydrocarbon residues include C_{1-3} alkyl groups substituted by halogen, hydroxy, amino, carboxyl, C_{1-6} alkoxy carbonyl. Examples of the substituted hydrocarbon residues include 2-hydroxyethyl, 2-aminoethyl, 2-fluoroethyl, 2-chloroethyl,

2-bromoethyl, carboxymethyl, 1-carboxy-1-methylethyl, 1-carboxycyclopropyl, 1-carboxycyclobutyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonyl-1-methylethyl, 1-ethoxycarbonyl-1-methylethyl, 1-tert-butoxycarbonyl-1-methyl-ethyl, 1-benzyloxycarbonyl-1-methylethyl, 1-pivaloyloxycarbonyl-1-methylethyl.

R_7 is hydrogen; C_{1-6} alkyl; C_{3-6} cycloalkyl; C_{6-10} aryl; C_{7-12} aralkyl; C_{1-6} alkoxy carbonyl C_{1-6} alkyl; carboxyl C_{1-6} alkyl; a five or six-membered heterocyclic group containing from 1 to 4 of any one or more of the heteroatoms selected from N, O and S (examples of which include but are not limited to pyridyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, isothiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, benzimidazolyl, triazolyl, tetrazolyl, and the like).

R_8 is also selected from the above mentioned substituents as defined for R_7 ; however, they may be the same or different.

R_7 and R_8 in the formula $CONR_7R_8$ may combine to form a heterocyclic ring which may contain at least another heteroatom selected from N, S or O (examples of which include but are not limited to piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, and the like). The said heterocyclic ring may be substituted at the carbon atom or at the nitrogen atom which is different from the nitrogen atom having binding arm with the CO group in the formula $CONR_7R_8$. Examples of such substituents include hydroxyl, hydroxy C_{1-4} alkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxy C_{1-4} alkyl, azido, cyano, halogeno C_{1-4} alkyl, carboxyl, carboxy C_{1-4} alkyl, C_{1-8} alkoxy carbonyl, C_{1-8} alkoxy carbonyl C_{1-4} alkyl, azido C_{1-4} alkyl, cyano C_{1-4} alkyl, amino, guanidino, amino C_{1-4} alkyl, mono- C_{1-4} alkylamino, di- C_{1-4} alkylamino, mono- C_{1-4} alkylamino C_{1-4} alkyl, di- C_{1-4} alkylamino C_{1-4} alkyl, halogen atom, carbamoyl, diethoxyphosphinyl C_{1-4} alkyl, dihydroxyphosphinyl C_{1-4} alkyl, mercapto, mercapto C_{1-6} alkyl, sulfo,

sulfo C_{1-4} alkyl, C_{1-6} alkylthio, C_{1-6} alkylthio C_{1-4} alkyl, C_{6-10} arylthio, C_{6-10} aryloxy carbonyl, C_{7-12} aralkyloxy carbonyl, C_{1-5} alkanoyl, C_{2-5} alkanoyl C_{1-4} alkyl, C_{2-5} alkanoyloxy, C_{2-5} alkanoyloxy C_{1-4} alkyl, or a heterocyclic group.

5 There may be the same or different plural of the above mentioned substituents, without limiting to the case of single substituent. The heterocyclic group means a 5- or 6-membered ring containing one to several heteroatoms, such as nitrogen atom (which may be oxidized), oxygen atom or sulfur
10 atom, or a condensed ring thereof, which possesses a binding arm at the carbon atom.

More specifically, the above substituents are: hydroxy, carboxy, tert-butoxycarbonyl, azido, amino hydroxymethyl, hydroxyethyl, bromoethyl, cyano, carboxamide,
15 guanidino, diethyl-phosphinylmethyl, diethylphosphinyethyl, dihydroxyphosphinyl-methyl, dihydroxyphosphinyethyl, 1,2,3-triazole, tetrazole.

In the structural formula (I), R_2 is hydrogen, chloro, bromo, fluoro, hydroxy, C_{1-6} alkoxy, trifluoromethyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, or $-CH_2X$,
20 wherein X is hydroxy, chloro, bromo, C_{1-6} alkoxy, C_{1-6} alkanoyloxy, $-OCONH_2$, $-OCONHC_{1-6}$ alkyl, amino, $-NHC_{1-6}$ alkyl, $-N(C_{1-6} \text{ alkyl})_2$, a quaternary ammonium group (for example, NH_3^+ , NHZ_2^+ , NZ_3^+ where Z represents lower alkyl, aryl or aralkyl;
25 the nitrogen atom may also be the part of the heterocyclic system).

In the structural formula (I), R_2 also represents $-CH_2YR_9$, wherein Y is S or N.

When Y is sulfur, R_9 may be hydrogen or the residue of a
30 thiol compound. The term "residue of a thiol compound" means a residue obtained by omitting the $-SH$ group from a thiol compound. Preferred thiol compounds are heterocyclic thiols. Examples of such heterocyclic groups that might be mentioned are: an unsaturated 5 to 8 membered heteromonocyclic group
35 containing at least one of the heteroatoms selected from N, O or S; an unsaturated 5 to 8 membered heteromonocyclic group containing 2 to 4 nitrogen atoms; an unsaturated 5 to 8

membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms; an unsaturated 5 to 8 membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms.

5 The above mentioned heterocyclic rings may be substituted further with one or more of the following radicals such as C_{1-6} alkyl, $-COOH$, $-COOC_{1-6}$ alkyl, $-OH$, $-CH_2COOH$, $-CH_2COOC_{1-6}$ alkyl halogen, or the like. The substituents may be at the carbon atom or at the nitrogen atom.

10 In the formula $-CH_2YR_9$, when Y is nitrogen, R_9 represents the residue of a nitrogen containing heterocyclic ring system. More specifically, Y together with R_9 forms a heterocyclic ring where Y is nitrogen which is part of the heterocyclic system. The above mentioned heterocycles may be further substituted with one or more of the functional groups selected from chloro, bromo, fluoro, hydroxy, carboxy, carbomethoxy, carboethoxy, cyano, amino, hydroxyalkyl, substituted amino, carboxamido and the like.

20 The preferred groups representing R_2 in the structure (I), include: hydrogen, chloro, bromo, hydroxy, methoxy, methyl, trifluoromethyl, vinyl, hydroxymethyl, chloromethyl, bromomethyl, azidomethyl, acyloxymethyl, carbamoyloxymethyl, 1,2,3-triazolylmethyl, 1,2,4-triazol-1-yl methyl, imidazol-1-yl methyl, pyrazol-1-yl methyl, thiazolylthiomethyl, isothiazolylthiomethyl, tetrazolylthiomethyl, triazinylthiomethyl, 1-substituted pyridinium-4-ylthiomethyl, 2,3-cyclopenteno-1-substituted pyridinium-4-ylthiomethyl, pyridyl-2-ylthiomethyl, pyridyl-4-ylthiomethyl, 1,3,4-thiadiazolylthiomethyl, 1,2,3-thiadiazolylthiomethyl, 1,2,4-thiadiazolylthiomethyl, 1H-1,2,3-triazolylthiomethyl, 4H-1,3,4-triazolylthiomethyl, 2H-1,2,4-triazolylthiomethyl, s-triazolo[1,5-a]pyrimidinylthiomethyl, 1H-triazolo[4,5-e]pyrimidinylthiomethyl, pyridinium methyl, 2,3-cyclopenteno pyridinium methyl, N-methylpyrrolidinium methyl, N-methylpiperidinium methyl.

Preferred substituents on the heterocyclic rings are: methyl, hydroxy, oxo, amino, carboxyl, carboxymethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonyl methyl, hydroxymethyl, hydroxyethyl, dimethylaminomethyl.

R_3 is hydrogen, C_{1-6} alkoxy, more preferably R_3 is methoxy and ethoxy.

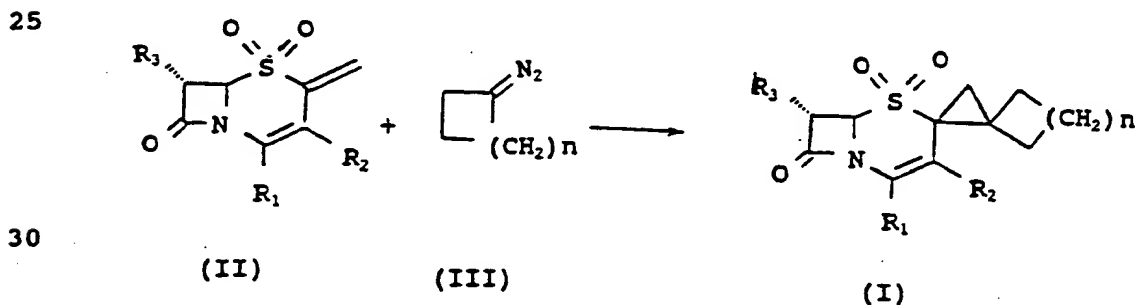
In the structural formula (I), n is 0, 1, 2, 3 or 4. More specifically, n is 1, 2, or 3.

The present invention also includes the salts of those compounds of cephem (I). Among the salts of the compound (I), especially pharmaceutically acceptable salts are used when the compound (I) is applied as an anti-elastase agent and other salts are utilized as intermediates for synthesis. Examples of the salts of compound (I) include the inorganic base salts, ammonium salts, organic base salts, basic amino acid salts, inorganic acid addition salts, organic acid addition salts. Inorganic bases that can form the inorganic base salts include alkaline metals (e.g. sodium, potassium) and alkaline earth metals (e.g. calcium, magnesium); organic bases that can form the organic base salts include procaine, 2-phenylethylbenzylamine, dibenzylethylene-diamine, ethanolamine, diethanolamine; inorganic acids that can form the inorganic acid addition salts include hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid; organic acids that can form the organic acid addition salts include p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid, acetic acid, formic acid, oxalic acid, maleic acid, succinic acid; basic amino acids that can form the basic amino acid salts include lysine, arginine, ornithine and histidine. Among these salts, the base salts (i.e. inorganic base salts, ammonium salts, organic base salts and basic amino acid salts) mean base salts which can be formed when an acid group such as carboxyl or sulfo group is present in the structural formula (I). The acid addition salts (i.e. inorganic acid addition salts and organic acid addition salts) mean acid addition salts which can be formed when a basic group, (such

as amino, piperazine, guanidino, monoalkylamino, di-alkylamino, cycloalkylamino, arylamino, cyclicamino or nitrogen - containing heterocyclic group) is present in the structural formula (I).

5 The present invention also includes those compounds of the structural formula (I) that have suitably pharmaceutically acceptable in vivo hydrolysable esters, namely those esters which hydrolyze in the human body to produce the parent acid or its salt. Examples of such
10 metabolically unstable, non-toxic esters include C₁₋₅ alkanoyloxymethyl ester, C₁₋₅ alkanoyloxyethyl ester, C₁₋₆ alkoxy C₁₋₄ alkyl ester or 1-(C₁₋₆ alkoxy-carbonyloxy) C₁₋₆ alkyl ester, more specifically acetoxymethyl ester, 1-acetoxyethyl ester, 1-acetoxybutyl ester, 2-acetoxyethyl ester,
15 pivaloyloxy-methyl ester, methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, ethoxycarbonyloxymethyl ester, 1-(ethoxycarbonyl)ethyl ester, tert-butoxycarbonyloxymethyl ester, 1-(tert-butoxycarbonyloxy)ethyl ester, and other such
20 ester groups which have been or can be used in the penicillin and cephalosporin art.

 The method for preparing the cephem sulfone (I) of this invention is described in the following process:

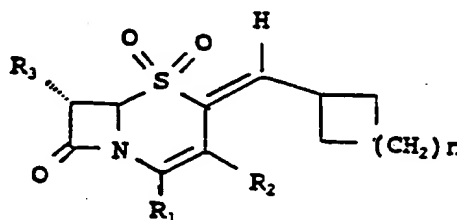
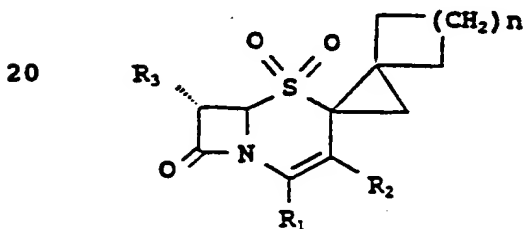


35 The starting compound (II) can be easily prepared by a known method [e.g. US Pat. Appln. No. 685,960 (pending), US Pat. Appln. No. 747,762 (pending), US Pat. Appln. No. 4,547,371] or one analogous thereto.

The cephem sulfone (I) can be prepared by carrying out a cycloaddition reaction of the compound (II) with a cycloalkyl diazo derivative of the formula (III) wherein the symbols have the same meaning as described before.

5 The diazo derivative (III) is usually used in an amount of 1 to 5 moles, preferably 1 to 2 moles, per 1 mole of the compound (II). The reaction is conducted at -40°C to 50°C , preferably at -30°C to 30°C , and most desirably at -10°C to 10°C . The reaction time varies depending on the
10 species of the compounds (II) and (III), the kind of solvent (also the mixing ratio, if a mixed solvent is used), the reaction temperature, etc., being usually 1 minute to 10 hours, preferably 15 minutes to 3 hours.

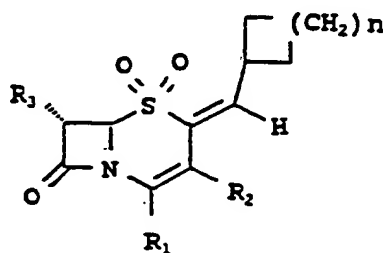
15 The present invention also includes the following compounds (IV), (V) and (VI) which are obtained from the cycloaddition reaction.



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More specifically, the most preferred embodiments of the present invention is comprised of the following compounds; but it should be understood that the present invention is not limited to such specific compounds.

10 t-Butyl 7 α -methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;

t-Butyl 7 α -methoxy-2-spiro(2'-spirocyclohexyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;

15 7 α -Methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-methyl-3-cephem-4-carboxylic acid -1,1-dioxide, and its sodium salt;

20 7 α -Methoxy-2-spiro(2'-spirocyclohexyl) cyclopropyl-3-methyl-3-cephem-4-carboxylic acid -1,1-dioxide, and its sodium salt;

25 7 α -Methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-methyl-3-cephem-4-[(4-N-methyl)piperazine]carboxamide]-1,1-dioxide, and its hydrochloride salt;

30 7 α -Methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-methyl-3-cephem-4-[(4-t-butoxycarbonyl)piperidine]carboxamide]-1,1-dioxide;

35 7 α -Methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-methyl-3-cephem-4-[(4-carboxy)piperidine]carboxamide]-1,1-dioxide, and its sodium salt;

- 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-N-t-
butoxycarbonylmethyl)piperazine]carboxamide]-1,1-
dioxide;
- 5
- 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-N-acetic
acid)piperazine]carboxamide]-1,1-dioxide, and its
sodium salt;
- 10
- 7 α -Methoxy-2-spiro(2'-spirocyclohexyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-N-
methyl)piperazine]carboxamide]-1,1-dioxide, and
its hydrochloride salt;
- 15
- 7 α -Methoxy-2-spiro(2'-spirocyclohexyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-N-t-
butoxycarbonyl methyl)piperazine]-carboxamide]-
1,1-dioxide;
- 20
- 7 α -Methoxy-2-spiro(2'-spirocyclohexyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-N-acetic
acid)piperazine]carboxamide]-1,1-dioxide, and its
sodium salt;
- 25
- t-Butyl 7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-
oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-
carboxylate-1,1-dioxide and its sodium salt;
- 30
- t-Butyl 7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(1-methyl-1,2,3,4-tetrazole-5-
yl)thiomethyl]-3-cephem-4-carboxylate-1,1-dioxide;
- 35
- t-Butyl 7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(2-methyl-1,3,4-thiadiazole-5-
yl)thiomethyl]-3-cephem-4-carboxylate-1,1-dioxide;

- t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(pyridyl-4-yl)thiomethyl]-3-cephem-
4-carboxylate-1,1-dioxide;
- 5 t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(pyridyl-2-yl)thiomethyl]-3-cephem-
4-carboxylate-1,1-dioxide;
- 10 t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-bromomethyl-3-cephem-4-carboxylate-
1,1-dioxide;
- 15 t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-acetoxymethyl-3-cephem-4-
carboxylate-1,1-dioxide;
- 20 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-
oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-
piperidine carboxamide-1,1-dioxide, and its sodium
salt;
- 25 7,7-Dihydro-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-
carboxy)piperidine]carboxamide]-1,1-dioxide, and
its sodium salt;
- 30 7,7-Dihydro-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(N-methyl-N-
acetic acid)]carboxamide-1,1-dioxide, and its
sodium salt;
- 35 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-
oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-
[(4-carboxy)piperidine]-carboxamide]-1,1-dioxide,
and its sodium salt;

- 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-methylcarbonyl-
1,1-dioxide;
- 5 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[4'-(methyl)-4'-
(methoxyimino)]-1,1-dioxide;
- 10 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-
carboxamide)piperidine]carboxamide]-1,1-dioxide;
- 15 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-
cyano)piperidine]carboxamide]-1,1-dioxide;
- 20 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-
hydroxy)piperidine]carboxamide]-1,1-dioxide;
- 25 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-
hydroxyethyl)piperidine]carboxamide]-1,1-dioxide;
- 30 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-
diethoxyphosphinyethyl)piperidine]-carboxamide]-
1,1-dioxide.

BIOLOGICAL EVIDENCE

- 35 The in vitro test data on anti-elastase activity of
exemplary derivatives having the structural formula I are
shown in Table I herebelow:

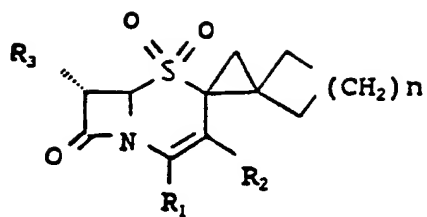
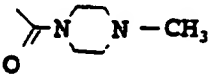
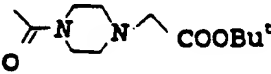
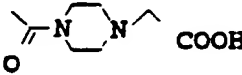
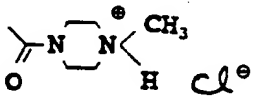
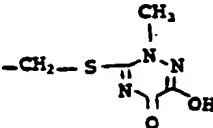
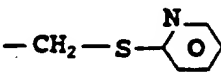
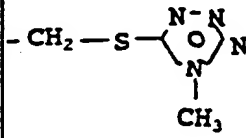
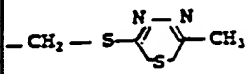
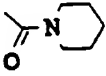
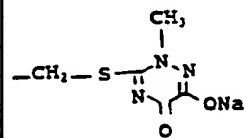
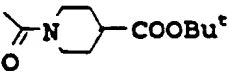
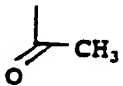
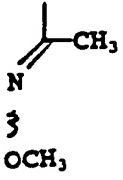
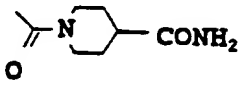
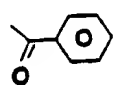
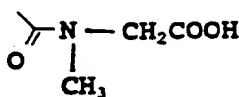
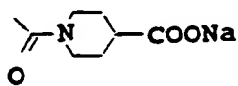
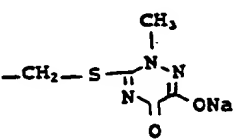


TABLE I
IC₅₀ VALUES OF 2-SPIRO(2'-SPIROCYCLOALKYL) CYCLOPROPYL
CEPHALOSPORIN SULFONES AGAINST HLE

COMPOUND	R ₁	R ₂	R ₃	n	IC ₅₀ (nM)
1	COOBu ^t	CH ₃	CH ₃ O	2	4.17
2		CH ₃	CH ₃ O	2	27.3
3		CH ₃	CH ₃ O	2	24.4
4		CH ₃	CH ₃ O	2	139.0
5		CH ₃	CH ₃ O	2	58.1
6	COOBu ^t	CH ₃	CH ₃ O	3	3.47

COMPOUND	R ₁	R ₂	R ₃	n	IC ₅₀ (nM)
7		CH ₃	CH ₃ O	3	6.40
8		CH ₃	CH ₃ O	3	8.37
9		CH ₃	CH ₃ O	3	27.0
10		CH ₃	CH ₃ O	3	8.4
11	COOBu ^t	CH ₂ OAc	CH ₃ O	2	9.1
12	COOBu ^t		CH ₃ O	2	15.0
13	COOBu ^t		CH ₃ O	2	9.4

COMPOUND	R ₁	R ₂	R ₃	n	IC ₅₀ (nM)
14	COOBu ^t		CH ₃ O	2	15.3
15	COOBu ^t		CH ₃ O	2	10.3
16			OCH ₃	2	32.4
17		CH ₃	H	2	870
18		CH ₃	OCH ₃	2	10.7
19		CH ₃	OCH ₃	2	80.7

COMPOUND	R ₁	R ₂	R ₃	n	IC ₅₀ (nM)
20		CH ₃	OCH ₃	2	8.4
21		CH ₃	OCH ₃	2	3.9
22	COOCHph ₂	CH ₃	H	2	478
23		CH ₃	OCH ₃	2	75
24			OCH ₃	2	34

ENZYME ASSAY FOR INHIBITION OF HLE

ENZYME: Purified elastase from human white blood cells.

SUBSTRATE: MeO-succinyl-L-alanyl-L-alanyl-L-prolyl-L-valine-p-nitroanilide

REACTION 10 mM phosphate buffer (pH 7.6)

MIXTURE: 500 mM NaCl

10% dimethylsulfoxide

0.35 mM substrate

The enzyme activity was determined by monitoring the increase in absorbance at 410 nm caused by the hydrolysis of chromogenic substrates. Inhibition of enzyme by the compounds described were determined after a 10 minute preincubation with the enzyme in the reaction mixture minus substrate. Reaction was initiated by the addition of substrate. The concentration of human leukocyte elastase used for assay was at 10 nM.

For therapeutic administration, a compound having the structural formula I, is used in the form of conventional pharmaceutical preparation which contains said compounds as an active ingredient in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparations may be in solid form such as capsule, tablet, ointment, etc. or in liquid form such as solution, suspension or emulsion. There may be included in the above preparation auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and the other commonly used additives.

In general, a daily dose of between 0.2 mg and 150 mg, or even more per kilogram of body weight, per day may be administered to a patient. However, the dose level may vary and will depend upon a variety of factors such as the activity of the specific compound employed, the age, body weight, sex, diet, time of administration, route of administration, etc.

The following examples are provided to demonstrate the operability of the present invention.

EXAMPLE 1

t-Butyl 7 α -methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

To a suspension of anhydrous magnesium sulfate (3.5 g) in ether (50 ml) cooled to -15°C was added silver oxide (5.10 g), followed by cyclopentanone hydrazone (2.16 g). A solution of potassium hydroxide in methanol (1 ml) was added

dropwise. Within three to five minutes, a deep red color was developed. The reaction mixture was filtered quickly through a small bed of Celite. To the filtrate, a solution of t-butyl 7 α -methoxy-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide in methylene chloride (100 ml) was added and the reaction mixture was stirred at room temperature for 2 hours. The mixture was filtered through Celite and the filtrate was concentrated to dryness which was purified over a silica gel column using a mixture of hexane-ethyl acetate.

The first eluting component was:

t-Butyl-7 α -methoxy-2(Z)-[(cyclopentyl)methylene]-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (1.23 g, 28.1%); ^1H NMR (CDCl_3): δ 6.35 (d, 1H, J=10.7 Hz); 5.23 (d, 1H, J=1.4 Hz); 4.67 (d, 1H, J=1.4 Hz); 3.68-3.84 (m, 1H); 3.57 (s, 3H); 2.07 (s, 3H); 1.55 (s, 9H); 1.25-1.80 (m, 8H).

The second eluting component was:

t-Butyl-7 α -methoxy-2-spiro(3'-spirocyclopentyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide. ^1H NMR (CDCl_3): δ 4.87 (d, 1H, J=1.5 Hz); 4.57 (d, 1H, J=1.5 Hz); 3.55 (s, 3H); 2.14 (s, 3H); 1.83 (d, 1H, J=6.4 Hz); 1.62-2.00 (m, 8H); 1.53 (s, 9H); 1.48 (d, 1H, J=6.4 Hz).

The third eluting component was:

t-Butyl-7 α -methoxy-2(E)-[(cyclopentyl)methylene]-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (0.41 g, 8.88%). ^1H NMR (CDCl_3): δ 6.73 (d, 1H, J=10.8 Hz); 4.96 (d, 1H, J=1.6 Hz); 4.63 (d, 1H, J=1.6 Hz); 3.48 (s, 3H); 2.75-2.88 (m, 1H); 2.23 (s, 3H); 1.48 (s, 9H); 1.18-2.07 (m, 8H).

The fourth eluting component was:

t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (1.65 g, 37.67%). ^1H NMR (CDCl_3): δ 5.10 (d, 1H, J=1.8 Hz); 4.57 (d, 1H, J=1.8 Hz); 3.56 (s, 3H); 1.95 (d, 1H, J=6.5 Hz); 1.76 (s, 3H); 1.56 (s, 9H); 1.60-1.96 (m, 9H).

EXAMPLE 2

t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-[(1-methyl-1,2,3,4-tetrazole-5-yl)thiomethyl]-3-cephem-4-carboxylate-1,1-dioxide

5

Step A:

To a solution of t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (Example 1, 761 mg, 1.9146 mmols) in carbon tetrachloride (35 ml) was added N-bromosuccinimide (374.8 mg, 2.1060 mmol) followed by AIBN (15.7 mg, 0.0957 mmols). The mixture was heated to reflux at 90°C for 21 hours; cooled to 0°C, the precipitated solid was removed by filtration. The filtrate was concentrated under reduced pressure to give a crude mass (1.15 g) which was chromatographed over a silica gel column using methylene chloride as eluant to give 670 mg (73.5%) of t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-bromomethyl-3-cephem-4-carboxylate-1,1-dioxide. ¹H NMR (CDCl₃): δ 5.14 (d, 1H, J=2.0 Hz); 4.60 (d, 1H, J=2.0 Hz); 4.35 (d, 1H, J=10.8 Hz); 3.57 (s, 3H); 3.32 (d, 1H, J=10.8 Hz); 2.16 (d, 1H, J=7.2 Hz); 1.65 (d, 1H, J=7.2 Hz); 1.60 (s, 9H); 1.55-2.00 (m, 8H).

Step B:

To a solution of t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-bromomethyl-3-cephem-4-carboxylate-1,1-dioxide (Example 2, step A; 100 mg, 0.2099 mmol) in acetonitrile (2 ml) was added 1-methyl-5-mercapto-1,2,3,4-tetrazole (24.38 mg, 0.2099 mmol) followed by triethylamine (64 μ l, 0.4618 mmol). After stirring at room temperature for 1 hour, the solvent was removed under reduced pressure and the residue was dissolved in methylene chloride; washed with dilute hydrochloric acid, followed by dilute sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated to give a brown foam which was purified over a silica gel column using hexane-ethyl acetate mixture as eluant to give the title compound as a yellow foam

(81 mg, 76%). ^1H NMR (CDCl_3): δ 5.12 (d, 1H, $J=1.9$ Hz); 4.60 (d, 1H, $J=1.9$ Hz); 4.26 (d, 1H, $J=13.0$ Hz); 3.92 (s, 3H); 3.80 (d, 1H, $J=13.0$ Hz); 3.58 (s, 3H); 1.72-1.97 (m, 10H); 1.59 (s, 9H).

5

EXAMPLE 3

t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-[(2-methyl-1,3,4-thiadiazole-5-yl)thiomethyl]-3-cephem-4-carboxylate-1,1-dioxide

10 To a solution of t-butyl-7 α -methoxy-2-spiro(2'-spirocyclo-pentyl)cyclopropyl-3-bromomethyl-3-cephem-4-carboxylate-1,1-dioxide (Example 2, Step A; 100 mg, 0.2099 mmol) in acetonitrile (2 ml) was added 5-methyl-2-mercapto-1,3,4-thiadiazole (27.7 mg, 0.2099 mmol), followed by
15 triethylamine (64 μL , 0.4618 mmol). After stirring at room temperature for 4 hours, the solvent was removed under reduced pressure and the residue was dissolved in methylene chloride, washed with dilute hydrochloric acid, dilute sodium bicarbonate solution, water and brine, dried over anhydrous
20 sodium sulfate and concentrated to give a brown foam which was purified over a silica gel column using hexane-ethyl acetate mixture as eluant to give 54 mg (50%) of the title compound as a light yellow foam. ^1H NMR (CDCl_3): δ 5.12 (d, 1H, $J=1.9$ Hz); 4.59 (d, 1H, $J=1.9$ Hz); 4.20 (d, 1H, $J=13.0$ Hz); 3.96 (d, 1H, $J=13.0$ Hz); 3.57 (s, 3H); 2.72 (s, 3H);
25 1.94 (d, 1H, $J=9.3$ Hz); 1.73-1.96 (m, 9H); 1.58 (s, 9H).

EXAMPLE 4

t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-[(pyridyl-2-yl)thiomethyl]-3-cephem-4-carboxylate-1,1-dioxide

30 To a solution of t-butyl-7 α -methoxy-2-spiro(2'-spirocyclo-pentyl)cyclopropyl-3-bromomethyl-3-cephem-4-carboxylate-1,1-dioxide (Example 2, Step A; 100 mg, 0.2099 mmol) in acetonitrile (2 ml) were added 2-mercapto pyridine (23.6 mg, 0.2099 mmol) and triethylamine (64 μL , 0.4618 mmol). The reaction was worked up in the same manner as
35

described in Example 3. The title compound was obtained as a white foam (54 mg, 51%). ¹H NMR (CDCl₃): δ 8.37-8.39 (m, 1H); 7.44-7.52 (m, 1H); 7.16-7.20 (m, 1H); 6.95-7.02 (m, 1H); 5.12 (d, 1H, J=1.9 Hz); 4.58 (d, 1H, J=1.9 Hz); 3.93 (ABq, 2H, J=13.25 and 22.15 Hz); 3.57 (s, 3H); 1.64-1.96 (m, 10H); 1.57 (s, 9H).

EXAMPLE 5

t-Butyl-7 α-methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-[(pyridyl-4-yl)thiomethyl]-3-cephem-4-carboxylate-1,1-dioxide

The reaction was done in the same manner as described in Example 4 by using 4-mercapto pyridine. The yield of the title compound was 60 mg (57.7%). ¹H NMR (CDCl₃): δ 8.42 (d, br, 2H); 7.14 (d, br, 2H); 5.14 (d, 1H, J=2.0 Hz); 4.61 (d, 1H, J=2.0 Hz); 4.15 (d, 1H, J=11.7 Hz); 3.58 (s, 3H); 2.93 (d, 1H, J=11.4 Hz); 2.075 (d, 1H, J=7.3 Hz); 1.56-2.06 (m, 8H); 1.536 (s, 9H); 1.43 (d, 1H, J=7.3 Hz).

20

EXAMPLE 6

t-Butyl-7 α-methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)-thiomethyl]-3-cephem-4-carboxylate-1,1-dioxide

25 Step A:

To a solution of t-butyl-7 α-methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-bromomethyl-3-cephem-4-carboxylate-1,1-dioxide (Example 2, Step A; 200 mg, 0.4198 mmol) in acetonitrile (5 ml) were added 2,5-dihydro-6-diphenylmethyloxy-2-methyl-3-mercapto-5-oxo-1,2,4-triazine (137 mg, 0.4198 mmol) and triethylamine (0.8396 mmol). The reaction mixture was stirred at room temperature overnight, diluted with ethyl acetate, washed with dilute hydrochloric acid, sodium bicarbonate solution, water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a light brown foam. The product was purified over a silica gel column using hexane-ethyl acetate mixture as eluant. The

yield of the title compound was 170 mg (56.3%). ¹H NMR (CDCl₃): δ 7.30-7.46 (m, 10H); 6.75 (s, 1H); 5.09 (d, 1H, J=2.0 Hz); 4.58 (d, 1H, J=2.0 Hz); 3.9 (ABq, 2H, J=13.2 and 23.0 Hz); 3.62 (s, 3H); 3.56 (s, 3H); 1.61-1.96 (m, 10H); 1.56 (s, 9H).

Step B:

To a stirred solution of t-butyl-7 α-methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-carboxylate-1,1-dioxide (from Step A, 146 mg, 0.2196 mmol) in dry methylene chloride (5 ml) was added trifluoroacetic acid (204 μL, 1.2 mmol). The mixture was stirred at room temperature for 2.5 hours. The solvent was removed under reduced pressure and the residue was diluted with ether and treated with hexane. The precipitated white solid was collected by filtration, 81 mg (75%). ¹H NMR (CDCl₃): δ 5.11 (d, 1H, J=1.9 Hz); 4.59 (d, 1H, J=1.9 Hz); 4.30 (s, br, 1H); 3.79 (ABq, 2H, J₁=13.2 Hz, J₂=28.3 Hz); 3.75 (s, 3H); 3.58 (s, 3H); 1.99 (d, 1H, J=7.0 Hz); 1.73-2.00 (m, 9H); 1.58 (s, 9H).

EXAMPLE 7

7 α-Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-carboxy)piperidine]carboxamide-1,1-dioxide

Step A:

A solution of t-butyl-7 α-methoxy-2-spiro(2'-spirocyclopentyl)-cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (Example 2, 0.50 g, 1.26 mmol) in formic acid (10 ml) was stirred at 50°C for a period of 1 hour and the formic acid was removed by freeze-drying. The residue was washed several times with a mixture of hexane-ether (9.5:0.5) and finally dissolved in methylene chloride. Evaporation of the solvent in vacuo gave a foam (0.408 g, 95%). ¹H NMR (CDCl₃): δ 8.03 (s, br, 1H); 5.13 (d, 1H,

J=1.6 Hz); 4.62 (d, 1H, J=1.6 Hz); 3.58 (s, 3H); 2.046 (d, 1H, J=6.6 Hz); 1.67 (d, 1H, J=6.6 Hz); 1.56-2.00 (m, 8H); 1.91 (s, 3H).

5 STEP B:

To a stirred and ice-cooled solution of 7 α -methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide (from Step A, 2.96 g, 8.7 mmol) in dry methylene chloride (100 ml) under nitrogen was added oxalyl chloride (1.46 g, 1.13 mmol) followed by four drops of dimethylformamide. The reaction mixture was stirred for 15 min. at 10°C and at room temperature for 50 min. Volatile materials were removed under reduced pressure. The solid obtained was dissolved in dry methylene chloride (100 ml). To this solution, a solution of 4-t-butoxycarbonyl piperidine (1.61 g, 8.7 mmol) in methylene chloride (5 ml) was added, followed by triethylamine (0.934 g, 9.1 mmol). The reaction mixture was stirred at room temperature for 1.5 hr, then diluted with 100 ml of methylene chloride. The methylene chloride solution was washed successively with sodium bicarbonate solution, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a light brown solid which was purified over a silica gel column using hexane-ethyl acetate mixture (3:2) as eluant. The title compound was obtained as a white solid (3.33 g, 75.5%). ¹H NMR (CDCl₃): δ 5.11-5.14 (m, 1H); 4.58-4.59 (m, 1H); 4.31-4.50 (m, 1H); 3.65-3.85 (m, 1H); 3.54 and 3.55 (2s, 3H); 2.90-3.20 (m, 2H); 2.35-2.55 (m, 1H); 1.50-2.04 (m, 14H); 1.58 (s, 3H); 1.45 (s, 9H).

30

Step C:

A solution of 7 α -methoxy-2-spiro(2'-spirocyclopentyl)cyclo-propyl-3-methyl-3-cephem-4-[(4-t-butoxycarbonyl)piperidine] carboxamide]-1,1-dioxide (3.2 g, 6.3 mmol) in anhydrous formic acid (200 ml) was stirred under nitrogen at 40-45°C over a period of 1.5 hours and formic acid was removed by freeze-drying. The residual mass was

35

digested with a mixture of hexane-ether (8.5:1.5); the precipitated solid was filtered off, 2.45 g (85.8%). ¹H NMR (CDCl₃): δ 5.13-5.15 (m, 1H); 4.60-4.61 (m, 1H); 4.25-4.55 (m, 1H); 3.5-3.90 (m, 1H); 3.54 (s, 3H); 2.90-3.25 (m, 2H);
5 2.50-2.75 (m, 1H); 1.51-2.10 (m, 14H); 1.53 and 1.58 (2s, 3H).

EXAMPLE 8

10 7 α-Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-N-methyl)piperazine]carboxamide]-1,1-dioxide hydrochloride

Step A:

To a stirred and ice-cooled solution of 7 α-methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide (Example 7, Step A; 2.75 g, 8.06 mmol) in dry methylene chloride (100 ml) under nitrogen was added oxalyl chloride (1.36 g, 10.5 mmol) followed by three drops of DMF. The reaction mixture was
20 stirred at 10°C for 15 min and then at room temperature for 50 min. The volatile solvents were removed under reduced pressure. The solid thus obtained was dissolved in 80 ml of dry methylene chloride and stirred under nitrogen. To the above solution was added a solution of N-methyl-piperazine
25 (0.824 g, 8.06 mmol) followed by triethylamine (0.865 g, 8.46 mmol). The reaction mixture was stirred at room temperature for one hour, then diluted with methylene chloride (100 ml); washed successively with sodium bicarbonate solution, brine, dried (Na₂SO₄) and concentrated to give a light yellow foam.
30 The product was purified over a silica gel column using ethyl acetate-methanol (9.5:0.5) as eluant; yield 1.96 g (57.5%). ¹H NMR (CDCl₃): δ 5.12 (d, 1H, J=1.9 Hz); 4.60 (d, 1H, J=1.9 Hz); 3.55 (s, 3H); 3.5-4.0 (m, 4H); 2.33-2.50 (m, 4H); 2.33 (s, 3H); 1.92 (d, 1H, J=6.4 Hz); 1.56-1.93 (m, 8H); 1.55 (s, 3H);
35 1.52 (d, 1H, J=6.4 Hz).

STEP B:

1.96 g (4.63 mmol) of 7 α -methoxy-2-spiro(2'-
spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-
5 methyl)piperazine}carboxamide]-1,1-dioxide (from the previous
step) was dissolved in dry methylene chloride (15 ml). A
stream of dry hydrogen chloride gas was bubbled through this
solution and the reaction mixture was stirred at room
temperature for 10 min. The reaction mixture was diluted
10 with 50 ml of anhydrous ether. The precipitated white solid
was collected by filtration, 1.9 g (89.2%). ¹H NMR (CDCl₃):
 δ 5.09 (d, 1H, J=1.7 Hz); 4.76-4.83 (m, 1H); 4.62 (d, 1H,
J=1.7 Hz); 3.30-4.20 (m, 5H); 3.56 (s, 3H); 2.90-3.10 (m,
2H); 2.81 (d, 3H, J=4.06 Hz); 1.96 (d, 1H, J=6.5 Hz); 1.55-
15 1.98 (m, 9H); 1.55 (s, 3H).

EXAMPLE 9

7 α -Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-
3-cephem-4-[(4-N-aceticacid)piperazine}carboxamide-1,1-
20 dioxide

STEP A:

To a stirred and ice-cooled solution of 7 α -methoxy-2-
spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-
25 carboxylic acid-1,1-dioxide (Example 7, Step A; 2.93 g, 8.6
mmol) in dry methylene chloride (100 ml) under nitrogen was
added oxalyl chloride (1.45 g, 11.2 mmol) followed by 4 drops
of DMF. The reaction mixture was stirred at 10°C for 15 min
and at room temperature for 45 min. The volatile materials
30 were removed under reduced pressure. The residual light
yellow foam was dissolved in methylene chloride and stirred
under nitrogen. To this reaction mixture was added 4-(t-
butoxycarbonyl methyl)piperazine (1.72 g, 8.6 mmol) dissolved
in methylene chloride (2 ml), followed by triethylamine
35 (0.923 g, 9.03 mmol). The reaction mixture was stirred at
room temperature for one hour and diluted with methylene
chloride (100 ml). The organic layer was washed with sodium

bicarbonate solution, brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a light yellow foam. Purification of the product over a silica gel column using hexane-ethyl acetate mixture as eluant gave the pure compound (3.3 g, 73.5%). ^1H NMR (CDCl_3): δ 5.09 (d, 1H, $J=2.0$ Hz); 4.56 (d, 1H, $J=2.0$ Hz); 3.80-4.00 (m, 1H); 3.51 (s, 3H); 3.4-3.7 (m, 3H); 3.12 (s, 2H); 2.56-2.70 (m, 4H); 2.26-2.40 (m, 1H); 1.62-1.98 (m, 10H); 1.52 (s, 3H); 1.43 (s, 9H).

10 STEP B:

7 α -Methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-methyl-3-cephem-4-[(4-N-t-butoxycarbonyl methyl)piperazine)-carboxamide]-1,1-dioxide (from Step A; 3.2 g, 6.1 mmol) was dissolved in anhydrous formic acid (150 ml) and the reaction mixture was stirred at 40-45°C for 2 hours. Formic acid was removed by freeze-drying. The residual gummy mass was digested with a mixture of hexane-ether (9:1). The precipitated solid was collected by filtration (2.06 g, 72%). ^1H NMR (CDCl_3): δ 5.4-5.5 (br, 1H); 5.11 (d, 1H, $J=2.0$ Hz); 4.60 (d, 1H, $J=2.0$ Hz); 4.1-4.2 (m, 1H); 3.5-3.75 (m, 3H); 3.55 (s, 3H); 3.32 (s, br, 2H); 2.70-3.05 (m, 4H); 1.52-1.95 (m, 10H); 1.56 (s, 3H).

EXAMPLE 10

25 t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclohexyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide

To a suspension of anhydrous magnesium sulfate (4.0 g) in dry ether (90 ml) cooled to -15°C was added silver oxide (8.11 g) followed by cyclohexanone hydrazone (3.75 g, 33.4 mmol). A solution of potassium hydroxide in methanol (1ml) was added dropwise. After stirring at this temperature for three minutes, a deep red color was formed. The reaction mixture was filtered rapidly through a small bed of Celite. To the filtrate a solution of t-butyl-7 α -methoxy-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (2.20 g, 6.7 mmol) in methylene chloride (50 ml) was added slowly. The reaction mixture was stirred at room temperature for 2

hours, concentrated under reduced pressure and the crude mass was purified over a silica gel column using hexane-ethyl acetate mixture (6:3) as eluant to give the pure compound (1.1 g, 40%). ¹H NMR (CDCl₃): δ 5.05 (d, 1H, J=2.0 Hz); 4.63 (d, 1H, J=2.0 Hz); 3.56 (s, 3H); 1.92 (s, 3H); 1.55 (s, 9H); 1.23-2.40 (m, 12H).

EXAMPLE 11

7α-Methoxy-2-spiro(2'-spirocyclohexyl)cyclopropyl-3-methyl-3-cephem-4-[(4-N-methyl)piperazine]carboxamide]-1,1-dioxide

STEP A:

t-Butyl-7 α-methoxy-2-spiro(2'-spirocyclohexyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (Example 10, 2.133 g, 5.18 mmol) was dissolved in anhydrous formic acid (40 ml) and the reaction mixture was stirred at 50°C for one hour. Formic acid was removed by freeze-drying. The residue thus obtained was digested with hexane; hexane layer was decanted off. This process was repeated several times and the residue was pumped out to give a foam (1.67 g, 91%). ¹H NMR (CDCl₃): δ 5.07 (d, 1H, J=2.0 Hz); 4.65 (d, 1H, J=2.0 Hz); 3.57 (s, 3H); 2.08 (s, 3H); 1.87 (d, 1H, J=6.4 Hz); 1.10-1.90 (m, 11H).

STEP B:

To a stirred and ice-cooled solution of 7 α-methoxy-2-spiro(2'-spirocyclohexyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide (from the previous step; 0.2 g, 0.62 mmol) in dry methylene chloride (5 ml) under nitrogen was added oxalyl chloride (0.092 g, 0.71 mmol), followed by 2 drops of DMF. The reaction mixture was stirred at room temperature for 50 min. The volatile materials were removed under reduced pressure. The residual light yellow foam was dissolved in methylene chloride (10 ml) and stirred under nitrogen at 0°C. To this solution, N-methylpiperazine (0.124 g, 1.24 mmol) was added. The reaction mixture was stirred at ice-temperature for 30 min. and at room

temperature for 30 min., diluted with 30 ml of methylene chloride. The methylene chloride layer was washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a crude product which was purified over a silica gel column using ethyl acetate-methanol mixture as the eluant (0.163 g, 60%). ^1H NMR (CDCl_3): δ 5.08 (d, 1H, $J=2.0$ Hz); 4.73 (d, 1H, $J=2.0$ Hz); 3.54 (s, 3H); 3.40-3.90 (m, 4H); 2.35-2.50 (m, 4H); 2.31 (s, 3H); 1.80 (d, 1H, $J=6.6$ Hz); 1.64 (s, 3H); 1.50 (d, 1H, $J=6.6$ Hz); 1.17-1.89 (m, 10H).

EXAMPLE 12

t-Butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-acetoxymethyl-3-cephem-4-carboxylate-1,1-dioxide

By using the same procedure as described in Example 1, but using t-butyl 7 α -methoxy-2-methylene-3-acetoxymethyl-3-cephem-4-carboxylate-1,1-dioxide, the title compound was prepared. ^1H NMR (CDCl_3): δ 5.13 (d, 1H, $J=2.0$ Hz); 4.60 (d, 1H, $J=12.7$ Hz); 4.60 (d, 1H, $J=2.0$ Hz); 4.27 (d, 1H, $J=12.7$ Hz); 3.57 (s, 3H); 2.08 (s, 3H); 2.01 (d, 1H, $J=6.9$ Hz); 1.55 (s, 9H); 1.50-1.99 (m, 9H).

EXAMPLE 13

7 α -Methoxy--spiro(2'-spirocyclopentyl)cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-piperidine carboxamide-1,1-dioxide

Step A:

To a stirred and ice-cooled solution of 7 α -methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid -1,1-dioxide (Example 7, Step A; 3.0 g, 8.8 mmol) in dry methylene chloride (60 ml) under nitrogen was added oxalyl chloride (1.45 g, 11.43 mmol) followed by three drops of DMF. The reaction mixture was stirred at 10°C for 15 min. and then at room temperature for 45 min. The volatile solvents were removed under reduced pressure. The resulting solid thus obtained was dissolved in methylene chloride. To this solution, a solution of piperidine (1.65

g, 19.4 mmol) in methylene chloride (2 ml) was added and the mixture was allowed to stir for 1 hour at room temperature. The reaction mixture was then diluted with methylene chloride and washed with water followed by brine, dried over anhydrous sodium sulphate. Evaporation of the solvent in vacuo gave a yellow foam, which was purified over a silica gel column. Gradient elution of the column with a mixture of hexane-ethyl acetate gave pure 7 α -methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-piperidine carboxamide-1,1-dioxide, as a white foam (2.5 g, 69.4%). ¹H NMR (CDCl₃): δ 5.12 (d, 1H, J=2.0 Hz); 4.60 (d, 1H, J=2.0 Hz); 3.62-3.72 (m, 2H); 3.55 (s, 3H); 3.37-3.45 (m, 2H); 1.92 (d, 1H, J=6.4 Hz); 1.58-1.84 (m, 14H); 1.56 (s, 3H); 1.51 (d, 1H, J=6.4 Hz).

15

Step B:

To a solution of 7 α -methoxy-2-spiro(2'-spirocyclopentyl)-cyclopropyl-3-methyl-3-cephem-4-piperidine carboxamide-1,1-dioxide (2.41 g, 5.9 mmol) in anhydrous carbon tetrachloride (60 ml) was added N-bromosuccinimide (1.16 g, 6.5 mmol) followed by azoisobutyronitrile (0.097 g, 0.59 mmol). The reaction mixture was refluxed at 80°C for 24 hr., cooled to room temperature and filtered through Celite. The filtrate was evaporated in vacuo to give a crude mass which was purified over a silica gel column. Gradient elution of the column with a mixture of hexane-ethyl acetate gave the pure product, 7 α -methoxy-2-spiro(2'-spirocyclopentyl) cyclopropyl-3-bromomethyl-3-cephem-4-piperidine carboxamide-1,1-dioxide (1.31 g, 45.5%). ¹H NMR (CDCl₃): δ 5.16 (d, 1H, J=2.2 Hz); 4.62 (d, 1H, J=2.0 Hz); 4.06 (d, 1H, J=11.6 Hz); 3.78-3.90 (m, 1H); 3.56 (s, 3H); 3.56-3.65 (m, 2H); 3.43 (d, 1H, J=11.6 Hz); 3.32-3.35 (m, 1H); 2.14 (d, 1H, J=7.1 Hz); 1.65 (d, 1H, J=7.1 Hz); 1.56-2.00 (m, 14H).

30

Step C:

To a solution of 7 α -methoxy-2-spiro(2'-
spirocyclopentyl)-cyclopropyl-3-bromomethyl-3-cephem-4-
5 piperidine carboxamide-1,1-dioxide (Example 13, Step B, 0.5
g, 1.03 mmol) in acetonitrile (15 ml) was added 2-methyl-3-
mercapto-5-oxo-6-diphenylmethoxy-1,2,4-triazine (0.67 g, 2.05
mmol) followed by triethylamine (0.228 g, 2.3 mmol). The
reaction mixture was stirred at room temperature for 16 hr.
10 and acetonitrile was evaporated in vacuo. The crude product
was purified over a silica gel column using hexane-ethyl
acetate mixture as eluant. The mass of the pure product was
0.417 g (56%). ¹H NMR (CDCl₃): δ 7.26-7.46 (m, 10H); 6.75
(s, 1H); 5.14 (br, s, 1H); 4.62 (d, 1H, J=2.0 Hz); 3.61 (s,
15 3H); 3.56 (s, 3H); 3.56-3.90 (m, 4H); 3.24-3.47 (br, m, 2H);
1.58-2.05 (m, 16H).

Step D:

To a stirred and ice-cooled solution of 7 α -
20 methoxy-2-spiro-(2'-spirocyclopentyl)cyclopropyl-3-[(2,5-
dihydro-6-diphenyl-methoxy-2-methyl-5-oxo-1,2,4-triazin-3-
yl)thiomethyl]-3-cephem-4-piperidinecarboxamide-1,1-dioxide
(Example 13, Step C, 377 mg, 0.52 mmol) in anhydrous
methylene chloride (4.5 ml) was added dry anisole (8.5 ml)
25 followed by trifluoroacetic acid (13 ml). The reaction
mixture was stirred at 0°C for 1 hr. and evaporated in vacuo.
The gummy residue was digested with a mixture of hexane-ether
(2:1). The precipitated solid was dissolved in methylene
chloride and evaporated in vacuo to give pure compound, 7 α -
30 methoxy-2-spiro(2'-spirocyclo-pentyl)cyclopropyl-3-[(2,5-
dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)
thiomethyl]-3-cephem-4-piperidine carboxamide-1,1-dioxide, as
a foam (260 mg, 89%). ¹H NMR (CDCl₃): δ 5.15 (d, 1H, J=2.0
Hz); 4.64 (d, 1H, J=2.0 Hz); 3.74 (s, 3H); 3.57 (s, 3H);
35 3.57-3.85 (m, 4H); 3.37-3.47 (br, m, 2H); 1.98 (d, 1H, J=6.8
Hz); 1.50-2.00 (m, 15H).

EXAMPLE 14**7,7-Dihydro-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-carboxy)piperidine]carboxamide]1,1-dioxide**

5

Step A:

To a suspension of anhydrous sodium sulphate (40 g) in ether (200 ml) cooled to -10°C was added silver oxide (12.45 g), followed by cyclopentanone hydrazone (5.28 g, 53.7 mmol). A solution of potassium hydroxide in methanol (2 ml) was added dropwise. Within 5 minutes a deep red color was developed. The reaction mixture was filtered quickly through a small bed of Celite. To the filtrate, a solution of benzhydryl 7,7-dihydro-2-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (11 g, 26.9 mmol), dissolved in a mixture of methylene chloride and ethyl acetate was added. The mixture was stirred at room temperature for 1 hr. Evaporation of the solvent under reduced pressure gave a white solid which, upon purification by silica gel column chromatography using a mixture of hexane-ethyl acetate as eluant, gave benzhydryl 7,7-dihydro-2-spiro(2'-spirocyclopentyl)-cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (4.60 g, 35.1%). ¹H NMR (CDCl₃): δ 7.26-7.38 (m, 10H); 6.99 (s, 1H); 4.65 (dd, 1H, J=2.4 and 4.9 Hz); 3.60 (dd, 1H, J=2.0 and 15.0 Hz); 3.42 (dd, 1H, J=4.0 and 15.0 Hz); 1.71 (s, 3H); 1.95 (d, 1H, J=6.6 Hz); 1.60 (d, 1H, J=6.6 Hz); 1.54-1.96 (m, 8H).

Step B:

A mixture of benzhydryl 7,7-dihydro-2-spiro(2'-spirocyclo-pentyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (3.0 g, 6.3 mmol) in methylene chloride (25 ml), anhydrous anisole (50 ml) and trifluoroacetic acid (75 ml) was stirred under nitrogen atmosphere at 0°C for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was digested with hexane. The precipitated solid was filtered off, washed with hexane and air dried to give a white solid

(1.89 g, 96.4%). ^1H NMR (CDCl_3): δ 6.45 (br, s, 1H); 4.70 (br, s, 1H); 3.44-3.55 (m, 2H); 1.91 (s, 3H); 1.67-2.00 (m, 10H).

5 Step C:

To a stirred and ice-cooled solution of 7,7-dihydro-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (Example 14, Step B, 1.29 g, 4.14 mmol) in anhydrous methylene chloride (25 ml) under nitrogen was added oxalyl chloride (0.684 g, 5.4 mmol) followed by two drops of DMF. The reaction mixture was stirred at room temperature for 1 hr. The volatile materials were removed under reduced pressure. The residue was dissolved in anhydrous methylene chloride and stirred under nitrogen. To this solution, a solution of 4-tert-butoxycarbonyl piperidine (0.768 g, 4.14 mmol) in methylene chloride (1 ml) was added in one portion followed by triethyl amine (0.44 g, 4.4 mmol). The reaction mixture was allowed to stir at room temperature for 1 hr., diluted with methylene chloride, washed successively with water, sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulphate, evaporated in vacuo to give the crude product which was purified by silica gel column chromatography using a mixture of hexane-ethyl acetate (1:4) as eluant. The pure compound, 7,7-dihydro-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-tert-butoxycarbonyl)piperidine]carboxamide]-1,1-dioxide was obtained as a foam (1.14 g, 60%). ^1H NMR (CDCl_3): δ 4.66 (dd, 1H, $J=2.4$ and 4.6 Hz); 4.28-4.53 (m, 1H); 3.75-3.97 (m, 1H); 3.53-3.67 (m, 1H); 3.37 (dd, 1H, $J=5.0$ and 16.2 Hz); 2.87-3.25 (m, 2H); 2.35-2.55 (m, 1H); 1.53 and 1.59 (2s, 3H); 1.50-2.10 (m, 14H); 1.45 (s, 9H).

35 Step D:

A mixture of 7,7-dihydro-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-tert-butoxycarbonyl)piperidine]carboxamide]-1,1-dioxide (Example

14, Step C, 0.4 g, 0.84 mmol) and anhydrous formic acid (15 ml) was stirred under nitrogen at 60°C for 2 hr. The reaction mixture was concentrated under reduced pressure and the residue was washed several times with hexane followed by a mixture of hexane-ether (1:1). The precipitated solid was filtered off and air dried to give the desired product (0.34 g, 96%). ¹H NMR (CDCl₃): δ 4.65 (dd, 1H, J=2.4 and 5.0 Hz); 4.20-4.60 (m, 1H); 3.75-4.00 (m, 1H); 3.59 (dd, 1H, J=2.4 and 16 Hz); 3.38 (dd, 1H, J=5.0 and 16 Hz); 3.10-3.30 (m, 2H); 2.90-3.10 (m, 1H); 2.50-2.75 (m, 1H); 1.53 and 1.59 (2s, 3H); 1.50-2.20 (m, 13H).

EXAMPLE 15

7,7-Dihydro-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(N-methyl-N-acetic acid)] carboxamide, 1,1-dioxide

Step A:

To a stirred and ice-cooled solution of 7,7-dihydro-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid -1,1-dioxide (Example 14, Step B, 0.51 g, 1.64 mmol) in anhydrous methylene chloride (15 ml) under nitrogen was added oxalyl chloride (0.27 g, 2.13 mmol) followed by two drops of DMF. The reaction mixture was then stirred at room temperature for 1 hr. and the volatile materials were removed under reduced pressure. The residue was redissolved in methylene chloride (15 ml) and stirred under nitrogen. A solution of tert-butylsarcosine (0.238 g, 1.64 mmol) in methylene chloride (1 ml) was added followed by triethylamine (0.174 g, 1.72 mmol) and the reaction mixture was stirred at room temperature for 1 hr. The mixture was diluted with methylene chloride (50 ml) and washed successively with water, sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulphate and evaporated in vacuo to give the crude product which was purified by silica gel column chromatography using a mixture of hexane-ethyl acetate (3:2) as eluant. The pure compound, 7,7-dihydro-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(N-methyl-N-t-butoxy-

carbonylmethyl)]carboxamide-1,1-dioxide was obtained as a white foam (0.33 g, 46%). ¹H NMR (CDCl₃): δ 4.89 (d, 1H, J=17.0 Hz); 4.66 (dd, 1H, J=2.5 and 5.03 Hz); 3.43 (d, 1H, J=17.0 Hz) 3.61 (dd, 1H, J=2.5 and 16.2 Hz); 3.38 (dd, 1H, J=5.0 and 16.2 Hz); 3.07 and 3.09 (2s, 3H); 1.53-2.05 (m, 9H); 1.90 (d, 1H, J=6.3 Hz); 1.74 (s, 3H); 1.47 (s, 9H).

Step B:

A mixture of 7,7-dihydro-2-spiro(2'-spiro-cyclopentyl)-cyclopropyl-3-methyl-3-cephem-4-[(N-methyl-N-t-butoxycarbonyl-methyl)]carboxamide-1,1-dioxide (Example 15, Step A, 0.3 g, 0.68 mmol) and anhydrous formic acid (10 ml) was stirred under nitrogen at 50°C for 3 hr. The reaction mixture was concentrated under reduced pressure and the residue was digested several times with hexane followed by a mixture of hexane-ether (3:2). The solid was filtered off and dried to give the pure product (0.19 g, 73%). ¹H NMR (CDCl₃): δ 5.20 (br, s, 1H); 4.69-4.75 (br, m, 2H); 3.35-3.91 (m, 3H); 3.13 (s, 3H); 1.68 (s, 3H); 1.57-1.90 (m, 10H).

EXAMPLE 16

7α-Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)-thiomethyl]-3-cephem-4-[(4-carboxy)piperidine]carboxamide-1,1-dioxide

Step A:

To a mixture of 7 α-methoxy-2-spiro(2'-spirocyclopentyl)-cyclopropyl-3-methyl-3-cephem-4-[(4-t-butoxycarbonyl)-piperidine]carboxamide]-1,1-dioxide (Example 7, Step B, 5.91 g, 11.6 mmol) and N-bromosuccinimide (2.38 g, 13.4 mmol) in carbon tetrachloride (200 ml) was added AIBN (0.19 g, 1.16 mmol) and the reaction mixture was heated at 100°C for 24 hr. The reaction mixture was cooled and filtered through Celite. The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography using a mixture of hexane-ethyl

acetate (7:3) to give the pure product (2.49 g, 37%). ¹H NMR (CDCl₃): δ 5.15 and 5.17 (2d, 1H, J=2.3 Hz each); 4.62 (d, 1H, J=1.7 Hz); 4.20-4.45 (m, 1H); 3.98-4.17 (m, 1H); 3.60-3.75 (m, 1H); 3.56 (s, 3H); 3.42 (d, 2H, J=11.6 Hz); 2.95-3.15 (m, 1H); 2.35-2.55 (m, 1H); 1.50-2.15 (m, 14H); 1.45 (s, 9H).

Step B:

To a solution of 7 α-methoxy-2-spiro(2'-spirocyclopentyl)-cyclopropyl-3-bromomethyl-3-cephem-4-[(4-t-butoxycarbonyl)-piperidine]carboxamide]-1,1-dioxide (Example 16, Step A, 1.5 g, 2.6 mmol) in acetonitrile (30 ml) was added 2-methyl-3-mercapto-5-oxo-6-diphenylmethoxy-1,2,4-triazine (2.08 g, 6.4 mmol) followed by triethylamine (0.797 g, 7.8 mmol). The mixture was stirred at room temperature for 72 hours. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using a mixture of hexane-ethyl acetate (1:1) to give the pure product (0.88 g, 41.5%). ¹H NMR (CDCl₃): δ 7.24-7.45 (m, 10H); 6.75 (s, 1H); 5.14 (d, 1H, J=2.0 Hz); 4.62 (d, 1H, J=2.0 Hz); 4.20-4.40 (m, 1H); 3.50-3.90 (m, 3H); 3.61 (s, 3H); 3.55 (s, 3H); 2.90-3.30 (m, 2H); 2.30-2.55 (br, m, 1H); 1.50-2.00 (m, 14H); 1.45 and 1.39 (2s, 9H).

Step C:

To a stirred and ice-cooled solution of 7 α-methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-[(2,5-dihydro-6-diphenylmethoxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-[(4-t-butoxycarbonyl)piperidine]carboxamide]-1,1-dioxide (Example 16, Step B, 0.836 g, 1 mmol) in dry methylene chloride (11 ml) was added dry anisole (20 ml) followed by trifluoroacetic acid (33 ml). The mixture was stirred at 0°C for 1 hr. and concentrated under reduced pressure. The residue was dissolved in small volume of methylene chloride and diluted with ether. The precipitated solid was filtered off and washed with hexane to

give the title compound as a white powder (0.579 g, 95%). ¹H NMR (CDCl₃): δ 5.16 (br, s, 1H); 4.66 (br, s, 1H); 4.30-4.45 (m, 1H); 3.75 and 3.77 (2s, 3H); 3.56 (s, 3H); 3.40-4.00 (m, 3H); 3.00-3.35 (m, 2H); 2.50-2.65 (m, 1H); 1.50-2.15 (m, 14H).

EXAMPLE 17

7 α-Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-methylcarbonyl-1,1-dioxide

To a stirred and ice-cooled solution of 7 α-methoxy-2-spiro-(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide (Example 7, Step A, 1.0 g, 2.929 mmol) in dry methylene chloride (20 ml) was added oxalyl chloride (332 μl, 3.808 mmol) followed by two drops of DMF, the reaction mixture was stirred at ice temperature for 15 min. and then at room temperature for 3 hr. Solvent was removed under reduced pressure. The residue was dissolved in dry THF (15 ml), cooled to -78°C, cuprous iodide (587 mg, 3.076 mmol) was added in one portion followed by methyl magnesium bromide (1.27 ml, 3(M) in ether); cooling bath was removed and the mixture was stirred for 2.5 hr. Saturated NH₄Cl (1 ml) was added slowly to the mixture and volatile materials were removed under reduced pressure. The residue was suspended in methylene chloride and filtered through a small bed of Celite. The filtrate was washed with aq. NaHCO₃ solution, brine, dried over anhydrous sodium sulphate and concentrated. The crude product (800 mg) was chromatographed on a silica gel column using hexane-ethyl acetate (2:1) mixture as eluant to afford a yellow foam which on treatment with ether gave the pure compound, 7 α-methoxy-2-spiro(2'-spirocyclopentyl)cyclo-propyl-3-methyl-3-cephem-4-methylcarbonyl-1,1-dioxide as a white foam (418 mg, 50% yield). ¹H NMR (CDCl₃): δ 5.12 (d, 1H, J=1.5 Hz); 4.62 (d, 1H, J=1.5 Hz); 3.58 (s, 3H); 2.48 (s, 3H); 1.98 (d, 1H, J=6.7 Hz); 1.72 (s, 3H); 1.61 (d, 1H, J=6.7 Hz); 1.50-1.99 (m, 8H).

EXAMPLE 18**7 α -Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[4'-(methyl)-4'-(methoxyimino)]-1,1-dioxide**

5 To a stirred suspension of 7 α -methoxy-2-spiro(2'-spirocyclo-pentyl)cyclopropyl-3-methyl-3-cephem-4-methylcarbonyl-1,1-dioxide (Example 17, 418 mg, 1.232 mmol) in a mixture of THF (8 ml) and ethanol (5 ml) was added pyridine (204 μ l, 2.524 mmol) and methoxylamine hydrochloride
10 (216 mg, 2.537 mmol). The mixture was stirred at room temperature for 4 days and then concentrated under reduced pressure. The residue was dissolved in EtOAc, then washed with water, dilute HCl, brine, dried over anhydrous Na₂SO₄, filtered and then concentrated to give a yellow foam (310
15 mg). The crude material was purified over a silica gel column using hexane-ethyl acetate mixture as eluant.

The fast eluting component was the minor isomer of 4-[4'-(methyl)-4'-(methoxyimino)]; 4 mg.

¹H NMR (CDCl₃): δ 4.84 (d, 1H, J=1.6 Hz); 4.53 (d, 1H, J=1.6 Hz); 3.95 (s, 3H); 3.58 (s, 3H); 2.03 (s, 3H); 1.92 (s, 3H); 1.79 (d, 1H, J=6.3 Hz); 1.50-1.90 (m, 8H); 1.43 (d, 1H, J=6.3 Hz).

The second major component was the major isomer of 4-[4'-(methyl)-4-(methoxyimino)]; 110 mg.

25 ¹H NMR (CDCl₃): δ 5.09 (d, 1H, J=1.9 Hz); 4.57 (d, 1H, J=1.9 Hz); 3.95 (s, 3H); 3.55 (s, 3H); 2.05 (s, 3H); 1.92 (d, 1H, J=6.5 Hz); 1.58 (s, 3H); 1.52 (d, 1H, J=6.5 Hz); 1.50-1.90 (m, 8H).

30

EXAMPLE 19**7 α -Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-carboxamide)piperidine]carboxamide]-1,1-dioxide**

35 By using the same procedure as described in Example 7, Step B, but using isonipecotamide instead of 4-t-butoxycarbonyl piperidine, the title compound was prepared.

¹H NMR (CDCl₃): δ 5.73 (br, 2H); 5.12 (d, 1H, J=1.6 Hz); 4.47-4.74 (m, 1H); 4.61 and 4.62 (2d, 1H, J=2.0 Hz); 3.70-4.00 (m, 1H); 3.55 and 3.54 (2s, 3H); 2.70-3.20 (m, 2H);
5 2.30-2.50 (m, 1H); 1.53-1.98 (m, 14H); 1.59 and 1.53 (2s, 3H).

EXAMPLE 20

10 7 α-Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-cyano)piperidine]carboxamide]-1,1-dioxide

A solution of 7 α-methoxy-2-spiro(2'-spirocyclopentyl)cyclo-propyl-3-methyl-3-cephem-4-[(4-carboxamide)piperidine]-carboxamide]-1,1-dioxide (Example 19, 100 mg, 0.23 mmol) in 5 ml of acetic anhydride was heated at
15 110-115°C for 18 hr. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride, washed with water aqueous NaHCO₃ solution, brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give a light yellow foam, 75 mg (75%).
20 ¹H NMR (CDCl₃): δ 5.13 and 5.12 (2d, 1H, J=1.9 Hz); 4.61 (d, 1H, J=1.9 Hz); 4.00-4.20 (m, 1H); 3.20-3.70 (m, 3H); 3.54 and 3.56 (2s, 3H); 2.90-3.00 (m, 1H); 1.60-2.10 (m, 14H); 1.53 and 1.56 (2s, 3H).

EXAMPLE 21

25 7 α-Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-hydroxy)piperidine]carboxamide]-1,1-dioxide

By using the same procedure as described in Example 7, Step B, but using 4-hydroxy piperidine instead of 4-t-butoxycarbonyl piperidine, the title compound was prepared.
30 ¹H NMR (CDCl₃): δ 5.12 and 5.13 (2d, 1H, J=1.7 Hz); 4.61 (d, 1H, J=1.7 Hz); 3.90-4.30 (m, 2H); 3.60-3.85 (m, 1H); 3.53 and 3.55 (2s, 3H); 3.15-3.40 (m, 2H); 1.48-2.00 (m, 14H); 1.54 and 1.57 (2s, 3H).

EXAMPLE 22

7 α -Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-hydroxyethyl)piperidine] carboxamide]-1,1-dioxide

5

By using the same procedure as described in Example 7, Step B, but using 4-hydroxyethyl piperidine instead of 4-t-butoxy-carbonyl piperidine, the title compound was prepared. ^1H NMR (CDCl_3): δ 5.12 (2d, 1H, $J=1.5$ Hz); 4.55-4.70 (m, 1H); 4.62 and 4.64 (2d, 1H, $J=1.9$ Hz); 3.75-3.98 (m, 1H); 3.71 (t, 2H, $J=6.4$ Hz); 3.53 and 3.54 (2s, 3H); 2.64-3.15 (m, 2H); 1.50-2.18 (m, 17H); 1.52 and 1.60 (2s, 3H).

10

EXAMPLE 23

7 α -Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-bromoethyl)piperidine]carboxamide]-1,1-dioxide

15

Bromine (23 μl , 0.45 mmol) was added to a vigorously stirred solution of triphenylphosphine (123 mg, 0.468 mmol) in 3 ml of dry CH_3CN . A solution of 7 α -methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-3-cephem-4-[(4-hydroxyethyl)-piperidine]carboxamide]-1,1-dioxide (Example 22, 200 mg, 0.442 mmol) in 2 ml of CH_3CN was added to the mixture and the mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure and the residue was purified over a silica gel column using hexane-ethyl acetate mixture as eluant. The title compound was obtained as a light yellow foam, 220 mg (97%). ^1H NMR (CDCl_3): δ 5.12 (d, 1H, $J=1.9$ Hz); 4.55-4.73 (m, 1H); 4.59 and 4.61 (2d, 1H, $J=2.0$ Hz); 3.70-3.90 (m, 1H); 3.54 (2s, 3H); 3.38-3.48 (m, 2H); 2.60-3.20 (m, 2H); 1.42-1.98 (m, 17H); 1.51 and 1.59 (2s, 3H).

20

25

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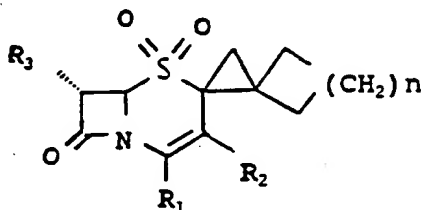
EXAMPLE 24

5 7 α -Methoxy-2-spiro(2'-spirocyclopentyl)cyclopropyl-3-methyl-
3-cephem-4-[(4-diethoxyphosphinyloethyl)piperidine]
carboxamide]-1,1-dioxide

10 A solution of 7 α -methoxy-2-spiro(2'-spiro-
cyclopentyl)-cyclopropyl-3-methyl-3-cephem-4-[(4-
bromoethyl)piperidine]-carboxamide (Example 23,
660 mg, 1.28 mmol) in 4.7 ml of triethyl phosphite was heated
at 110°C for 18 hr. Excess triethyl phosphite was removed
under reduced pressure and the residue was purified over a
silica gel column using ethyl acetate-methanol mixture as
eluant to afford the product as a white foam; 300 mg (41%).
15 ¹H NMR (CDCl₃): δ 5.12 and 5.13 (2d, 1H, J=1.7 Hz); 4.56-
4.70 (m, 1H); 4.60 and 4.61 (2d, 1H, J=1.9 Hz); 4.02-4.17 (m,
4H); 3.70-3.95 (m, 1H); 3.54 and 3.55 (2s, 3H); 2.58-3.15 (m,
2H); 1.50-2.00 (m, 19H); 1.51 and 1.59 (2s, 3H); 1.32 (t, 6H,
J=7.0 Hz).

What is claimed is:

1. A 7 α -substituted 2-spiro(2'-spirocycloalkyl) cyclopropyl cephalosporin sulfone of the structural formula (I)



.... (I)

wherein R₁ is COOR₄, COR₅, C(R₅)=N-OR₆ in which OR₆ is in the "syn" configuration or the "anti" configuration, CONR₇R₈;

R₄ is hydrogen; C₁₋₆ branched or straight chain alkyl; C₂₋₆ alkenyl; C₁₋₆ alkanoyl C₁₋₆ alkyl; C₁₋₆ alkanoyloxy C₁₋₆ alkyl; C₁₋₆ alkoxy C₁₋₆ alkyl; halogenated C₁₋₆ alkyl; -CH₂-phenyl; -CH(phenyl)₂; the phenyl groups being unsubstituted or substituted with at least one of C₁₋₆ alkyl, C₁₋₆ alkoxy, and nitro;

R₅ is hydrogen; C₁₋₆ straight or branched chain alkyl; C₂₋₆ alkenyl; C₂₋₆ alkynyl; C₃₋₆ cycloalkyl; C₆₋₁₀ aryl; aralkyl; a monocyclic or fused polycyclic saturated or unsaturated heterocyclic group containing from 1 to 4 of any one or more of the heteroatoms selected from N, S and O;

R₆ is hydrogen or a hydrocarbon residue which is unsubstituted or substituted at one or more positions with one or more hydrocarbon residue substituents which are the same or different;

R₇ and R₈ are the same or different, and are selected from hydrogen; C₁₋₆ alkyl; C₃₋₆ cycloalkyl; C₆₋₁₀ aryl; C₇₋₁₂ aralkyl; C₁₋₆ alkoxy carbonyl C₁₋₆ alkyl; carboxyl C₁₋₆ alkyl; a five or six-membered heterocyclic group containing from 1 to 4 of any one or more of the heteroatoms selected from N, S and O;

or R_7 and R_8 in the formula CONR_7R_8 may combine to form a heterocyclic ring component which may contain at least one other heteroatom selected from N, S and O, said heterocyclic ring component being unsubstituted or substituted, with one or more substituents which are the same or different, at the carbon atom or at the nitrogen atom which is different from the nitrogen atom having a binding arm with the CO group in the formula CONR_7R_8 ;

R_2 is hydrogen, chloro, bromo, fluoro, hydroxy, C_{1-6} alkoxy, trifluoromethyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, or $-\text{CH}_2\text{X}$

wherein X is hydroxy, chloro, bromo, C_{1-6} alkoxy, C_{1-6} alkanoyloxy, $-\text{OCONH}_2$, $-\text{OCONHC}_{1-6}$ alkyl, amino, $-\text{NHC}_{1-6}$ alkyl, $-\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, or a quaternary ammonium group;

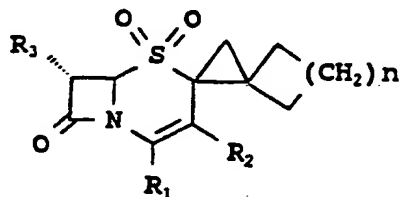
or R_2 is $-\text{CH}_2\text{YR}_9$, wherein Y is S or N, wherein when Y is sulfur, R_9 is hydrogen or the residue of a thiol compound obtained by omitting the $-\text{SH}$ group from a thiol compound, and when Y is nitrogen, R_9 is the residue of a nitrogen-containing heterocyclic ring system in which Y together with R_9 forms a heterocyclic ring;

n is 0, 1, 2, 3 or 4;

R_3 is hydrogen or C_{1-6} alkoxy;

or a pharmaceutically acceptable salt or ester thereof.

2. A 7 α -substituted 2'-spirocycloalkyl-2-spirocyclopropyl cephalosporin sulfone of formula (I)



.... (I)

wherein R_1 is COOR_4 , COR_5 , $\text{C}(\text{R}_5)=\text{N}-\text{OR}_6$, CONR_7R_8 ;

R_4 is hydrogen, C_{1-6} alkyl or $-\text{CH}(\text{phenyl})_2$

R_5 is hydrogen, C_{1-6} alkyl or C_{6-10} aryl

R_6 is hydrogen or C_{1-6} alkyl

5 R_7 and R_8 are the same or different and are hydrogen, C_{1-6} alkyl or carboxyl C_{1-6} alkyl

or NR_7R_8 in the formula CONR_7R_8 is monocyclic heterocyclic ring group which has 1 or 2 nitrogen atom as hetero atom in its ring structure and which is unsubstituted or substituted with hydroxy, cyano, carboxamide, $-\text{COOC}_{1-6}$ alkyl, $-\text{COOH}$ or C_{1-6} alkyl which is unsubstituted or substituted by hydroxy, halogen, diethylphosphinyl, $-\text{COOC}_{1-6}$ alkyl or $-\text{COOH}$

15 R_2 is C_{1-6} alkyl which is unsubstituted or substituted by halogen or C_{2-6} alkanoyloxy or R_2 is $-\text{CH}_2\text{SR}_9$;

R_9 is a heterocyclic ring group which is unsubstituted or substituted with one or more radicals selected from C_{1-6} alkyl, $-\text{COOH}$, $-\text{COOC}_{1-6}$ alkyl, $-\text{OH}$, $-\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{COOC}_{1-6}$ alkyl or halogen;

20 R_3 is hydrogen or C_{1-6} alkoxy

n is 0, 1, 2, 3, or 4,

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 which is
25 selected from the group consisting of:

t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;

30 t-butyl-7 α -methoxy-2-spiro(2'-spirocyclohexyl)
cyclopropyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide;

7 α -Methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide
35 and its sodium salt;

7 α -Methoxy-2-spiro(2'-spirocyclohexyl)cyclopropyl-
3-methyl-3-cephem-4-carboxylic acid-1,1-dioxide and its
sodium salt;

5

t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-acetoxymethyl-3-cephem-4-carboxylate-1,1-
dioxide;

10

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-N-methyl)piperazine]
carboxamide]-1,1-dioxide and its hydrochloride salt;

15

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-t-butoxycarbonyl)
piperidine]carboxamide]-1,1-dioxide;

20

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-carboxy)piperidine]
carboxamide]-1,1-dioxide and its sodium salt;

25

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-N-t-butoxycarbonyl-
methyl)piperazine]carboxamide]-1,1-dioxide;

30

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-N-acetic acid)
piperazine]carboxamide]-1,1-dioxide and its sodium salt;

35

7 α -methoxy-2-spiro(2'-spirocyclohexyl)cyclopropyl-
3-methyl-3-cephem-4-[(4-N-methyl)piperazine]carboxamide]-
1,1-dioxide and its hydrochloride salt;

7 α -methoxy-2-spiro(2'-spirocyclohexyl)cyclopropyl-
3-methyl-3-cephem-4-[(4-N-t-butoxycarbonylmethyl)piperazine]
carboxamide]-1,1-dioxide;

7 α -methoxy-2-spiro(2'-spirocyclohexyl)cyclopropyl-
3-methyl-3-cephem-4-[(4-N-acetic acid) piperazine]
carboxamide]-1,1-dioxide and its sodium salt;

5

t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-bromomethyl-3-cephem-4-carboxylate-1,1-dioxide;

10 t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-
triazin-3-yl)thiomethyl]-3-cephem-4-carboxylate-1,1-dioxide
and its sodium salt;

15 t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(1-methyl-1,2,3,4-tetrazole-5-yl)thiomethyl]-
3-cephem-4-carboxylate-1,1-dioxide;

20 t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(2-methyl-1,3,4-thiadiazole-5-yl)thiomethyl]-
3-cephem-4-carboxylate-1,1-dioxide;

25 t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(pyridyl-2-yl)thiomethyl]-3-cephem-4-
carboxylate-1,1-dioxide;

t-butyl-7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(pyridyl-4-yl)thiomethyl]-3-cephem-4-
carboxylate-1,1-dioxide;

30 7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-
triazin-3-yl)thiomethyl]-3-cephem-4-piperidine carboxamide-
1,1-dioxide, and its sodium salt;

35 7,7-dihydro-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-carboxy)piperidine]
carboxamide]-1,1-dioxide, and its sodium salt;

7,7-dihydro-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(N-methyl-N-acetic acid)]
carboxamide-1,1-dioxide, and its sodium salt;

5

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-
triazin-3-yl)thiomethyl]-3-cephem-4-[(4-carboxy)piperidine]-
carboxamide]-1,1-dioxide, and its sodium salt;

10

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-methylcarbonyl-1,1-dioxide;

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
15 cyclopropyl-3-methyl-3-cephem-4-[4'-(methyl)-4'-
(methoxyimino)]-1,1-dioxide;

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-carboxamide)piperidine]
20 carboxamide]-1,1-dioxide;

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-cyano)piperidine]
carboxamide]-1,1-dioxide;

25

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[(4-hydroxy)piperidine]
carboxamide]-1,1-dioxide;

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
30 cyclopropyl-3-methyl-3-cephem-4-[(4-hydroxyethyl)
piperidine]carboxamide]-1,1-dioxide;

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
35 cyclopropyl-3-methyl-3-cephem-4-[(4-bromoethyl)piperidine]
carboxamide]-1,1-dioxide; and

7 α -methoxy-2-spiro(2'-spirocyclopentyl)
cyclopropyl-3-methyl-3-cephem-4-[[{(4-diethoxyphosphinyl-
ethyl)piperidine)-carboxamide]-1,1-dioxide.

5

4. A compound as recited in claim 1, wherein said
hydrocarbon residue substituent is selected from the group
consisting of C₃₋₆ cycloalkyl, carboxyl, C₁₋₈ alkoxy carbonyl,
C₆₋₁₀ aryl, a five or six-membered heterocyclic group
10 containing from 1 to 4 of any one or more of the heteroatoms
selected from N, S and O.

5. A compound as recited in claim 1, wherein R₇
and R₈ in the formula CONR₇R₈ combine to form a heterocyclic
15 ring component which may contain at least one other
heteroatom selected from N, S and O, said heterocyclic ring
component being substituted with one or more substituents
selected from the group consisting of hydroxy, carboxy, tert-
butoxycarbonyl, azido, amino, hydroxymethyl, hydroxyethyl,
20 bromoethyl, bromomethyl, cyano, carboxamide, guanidino,
diethylphosphinylmethyl, diethylphosphinyethyl,
dihydroxyphosphinylmethyl, dihydroxyphosphinyethyl, 1,2,3-
triazole, tetrazole, C₁₋₆ alkylthio C₁₋₄ alkyl,
C₆₋₁₀ arylthio C₁₋₄ alkyl, and heteroarylthio C₁₋₄ alkyl.

25

6. A compound as recited in claim 1, wherein said
quaternary ammonium group is selected from the group
consisting of NH_3^+ , NHZ_2^+ , NZ_3^+ , where Z is lower alkyl, aryl or
aralkyl, or a heterocyclic system containing a nitrogen atom.

30

7. A compound as recited in claim 1, wherein said
thiol compound is a heterocyclic thiol.

8. A compound as recited in claim 1, wherein n is
35 1, 2 or 3.

9. A compound as recited in claim 1, wherein R₃ is methoxy or ethoxy.

5 10. A compound as recited in claim 1, wherein said hydrocarbon residue is C₁₋₆ straight or branched chain alkyl, C₂₋₆ alkenyl or C₃₋₆ cycloalkyl.

10 11. A pharmaceutical composition for controlling inflammatory or degenerative conditions in a mammal comprising an effective amount of at least one 2-spiro(2'-spirocycloalkyl)cyclopropyl cephalosporin sulfone of the structural formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or ester thereof, in
15 admixture with a pharmaceutically acceptable carrier.

12. A method of treating inflammatory or degenerative conditions which comprises administering to a patient in need of such treatment an effective amount of a
20 cephalosporin sulfone of the formula (I) as defined in claim 1.

13. A method as recited in claim 12, wherein said patient is an animal or a human being.

25

INTERNATIONAL SEARCH REPORT

Int. National Application No.

PCT/CA 94/00669

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D501/62 A61K31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 04977 (SYNPHAR LABORATORIES INC.) 18 April 1991 *Page 69-75: claims* ---	1,11
A	WO,A,92 17482 (SYNPHAR LABORATORIES INC.) 15 October 1992 *Page 33-41: claims* ---	1,11
A	WO,A,92 18474 (SYNPHAR LABORATORIES INC.) 29 October 1992 *Page 60-64: claims* ---	1,11
A	CHEMICAL ABSTRACTS, vol. 86, no. 7, 14 February 1977, Columbus, Ohio, US; abstract no. 43721d, page 539 ;column L ; see abstract & JP,A,7 676 285 (TEIJIN LTD.) 1 July 1976 --- -/--	1,11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

1 March 1995

Date of mailing of the international search report

- 9. 03. 95

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Authorized officer

Luyten, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 94/00669

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 86, no. 11, 14 March 1977, Columbus, Ohio, US; abstract no. 72670s, page 621 ;column L ; see abstract & JP,A,7 680 890 (TEIJIN LTD.) 15 July 1976</p> <p>-----</p>	1,11

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 12 and 13 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 94/00669

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9104977	18-04-91	AU-A- 6513190	28-04-91
		CA-A- 2067803	07-04-91
		EP-A- 0494914	22-07-92
		JP-T- 5503290	03-06-93
		US-A- 5264430	23-11-93
		US-A- 5264429	23-11-93

WO-A-9217482	15-10-92	US-A- 5258377	02-11-93
		AU-A- 1556092	02-11-92
		CA-A- 2107892	09-10-92
		EP-A- 0580650	02-02-94
		HU-A- 66046	28-09-94
		JP-T- 6506207	14-07-94

WO-A-9218474	29-10-92	US-A- 5264430	23-11-93
		US-A- 5264429	23-11-93
		AU-A- 1561292	17-11-92
		CA-A- 2107891	09-10-92
		EP-A- 0581789	09-02-94
		HU-A- 66140	28-09-94

JP-A-7676285		NONE	

JP-A-7680890		NONE	

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